How to assess survival prognosis in patients hospitalized for community-acquired pneumonia in 2024?

Julio A. Ramirez[a] *and Thomas M. File*[b]

Purpose of review
Community-acquired pneumonia (CAP) is increasingly recognized as a complex, multisystemic disease with the potential to cause both acute and long-term sequelae, significantly impacting patient mortality rates. In this manuscript, the authors review the current methodologies for assessing mortality risk among CAP patients.

Recent findings
The most common prediction scores for ICU care and short-term mortality include Pneumonia Severity Index (PSI), CURB-65, SMART COP, SCAP, and ATS/IDSA criteria. These models have clinical utility in the prediction of short-term mortality, but they have significant limitations in addressing long-term mortality. For patients who are discharged alive from the hospital, we do not have scores to predict long term mortality.

Summary
The development of an optimal prognostic tool for postacute sequelae of CAP is imperative. Such a tool should identify specific populations at increased risk. Moreover, accurately identifying at-risk populations is essential for their inclusion in clinical trials that evaluate potential therapies designed to improve short and long-term clinical outcomes in patients with CAP.

Keywords
community-acquired pneumonia, long-term mortality, scores to assess survival, short-term mortality

INTRODUCTION

Negative clinical outcomes in patients with community-acquired pneumonia (CAP) are not confined to the acute phase of the disease but may also occur months or years later [1]. It has become increasingly evident that CAP should be regarded as a multisystemic disease with potential for acute sequelae and long-term or chronic sequelae [2▪▪]. The impact of CAP on short-term mortality, define as mortality during hospitalization or within 30 days, is substantial. In the United States, approximately 650 out of every 100 000 adults are hospitalized with CAP annually, translating to approximately 1.5 million unique patients hospitalized due to CAP each year [3]. Considering that 9% of these patients are rehospitalized with CAP during the same year, the annual number of hospitalizations for CAP in the United States correspond to more than 1.7 million hospitalizations [3]. Data from United States and Germany indicate in hospital mortality ranging from 6.5% to 18.5%, and 30-day mortality ranging from 13% to 22.9% [3,4]. Studies evaluating long-term mortality in hospitalized patients with CAP using control groups of patients without CAP have documented decreased survival for patients with CAP when compared to controls [5–8]. In one of these studies, the population of patients discharged from the hospital due to medical conditions other than CAP reach 50% mortality 7 years after hospital discharged, while the population discharged from the hospital due to CAP reach 50% mortality within just 3 years post-discharge [8]. In this paper, the authors review how to assess survival prognosis for short-term mortality and long-term mortality among patients with CAP.

[a]Chief Scientific Officer, Norton Infectious Diseases Institute, Norton Healthcare, Louisville, Kentucky, USA and [b]Distinguished Physician, Infectious Disease Division, Summa Health, Akron, Ohio, USA

Correspondence to Julio A. Ramirez, Chief Scientific Officer, Norton Infectious Diseases Institute, Norton Healthcare, Louisville, KY, USA. Tel: +1 502 608 9044; e-mail: j.ramirez@louisville.edu

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KEY POINTS

- Community-acquired pneumonia cause both acute and long-term sequelae.
- Patients with community-acquired pneumonia are at risk for short-term and long-term mortality.
- Severity scores such as Pneumonia Severity Index and CURB-65 can be used to define the risk for short-term mortality.
- New tolls need to be developed to identify patients at risk for long-term mortality.

RISK FACTORS AND ASSESSMENT OF SHORT-TERM MORTALITY

Comorbidities

The presence of comorbid conditions in patients admitted to the hospital for CAP is strongly associated with severity of disease and short-term mortality [9]. Preexisting comorbidities including chronic respiratory, cardiovascular diseases and diabetes mellitus increase the risk of early mortality as they may predispose to further organ dysfunction.

In the derivation of the PORT score, Fine *et al.* identified age, sex, nursing home residence, and six coexisting illnesses (neoplastic disease, congestive heart failure, cerebrovascular disease, coronary artery disease, renal disease, and liver disease) plus hyperglycemia as independent predictors of 30 day mortality [10]. In a multicenter evaluation of hospitalized patients for CAP, Luna *et al.* found preexisting comorbidities independently associated with mortality were malignant disease, congestive heart failure, cerebrovascular accident, renal disease, and diabetes mellitus, and being age 80 years and older [11]. Blanc *et al.* observed the number of combined comorbidities impact the outcome of hospitalized CAP [12].

Preexisting comorbidities are associated with increased admission to ICUs and early mortality for patients with severe CAP (sCAP). Having a comorbidity approximately doubles the risk of ICU admission [13]. Cavallazzi *et al.* demonstrated the incidence of ICU admission increases with aging and the presence of comorbidities, of which congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes and renal disease have the highest impact [14]. While the Charlson score (which includes smoking and dementia in addition to other comorbidities) was derived based on a 1 year mortality, Bahlis *et al.* found it also correlated with in-hospital mortality [15,16]. Cilloniz *et al.* reported comorbidities in critically ill older patients is associated with longer hospital stays, ICU admission, hospital readmission and mortality [17]. Increased frailty as assessed by a risk score was also associated with higher 30-day mortality [18]. Data from patients admitted to intensive care units with COVID-19 found that a patient's age and comorbidity burden influenced mortality [19,20].

Severity of disease

Severity of infection is influenced by a combination of factors including host susceptibility and preexisting organ dysfunction, amount and virulence of a pathogen, and inflammatory immune response. Cytotoxic products released by pathogens initiate inflammatory host responses that contribute to the severity of illness and correlate to early mortality. In some patients, this initial response can become dysregulated producing tissue injury and acute organ dysfunction. In a study to compare systemic and local cytokine profiles and neutrophil responses in patients with severe versus nonsevere CAP, Fernandez-Botran *et al.* found that patients with severe CAP fail to mount a robust local pro-inflammatory response but exhibit instead a more substantial systemic inflammatory response, suggesting that a key driver of CAP severity may be the ability of the patient to generate an optimal local inflammatory response [21]. Markers of severity include WBC, Platelet count; $PaCO_2 < 35$ mmHg; multilobar pneumonia; bacteremia; shock; pH < 7.35 Hypalbuminemia; deceased BP; and hypoxemia [22].

Scores to predict short-term mortality

Several Clinical prediction scoring systems have been developed to predict ICU care and early mortality of patients who develop CAP. The most common include Pneumonia Severity Index (PSI), CURB-65, SMART COP, SCAP, and ATS/IDSA criteria [10,23–26]. Table 1 lists the values used to assess the scores and corresponding mortality rates at the higher scores. PSI is most comprehensive as it assesses 20 variables and therefore may be considered complex by clinicians, but scoring can be simplified by use of an online calculator tool. Also since age is a major component of the PSI score, it may underestimate the need for ICU care and mortality in younger age patients who present with severe manifestations of infection. Studies differ as to the predicting accuracy of the PSI vs. CURB-65. In a prospective study of 3181 patients with CAP, Aujesky *et al.* found the PSI had a higher discriminatory power for short-term mortality [27]. Another recent study found both PSI and CURB-65 showed a high strength in identifying high-risk patients; however,

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Table 1. Severity assessment scores for severe CAP

Score	PSI (Fine *et al.* 1997)	CURB-65 (Lim *et al.* 2003)	ATS/IDSA (Metlay *et al.* 2019)	SMART-COP (Charles *et al.* 2008)	SCAP (Espana *et al.* 2006)
Variables	Age Sex Comorbidities Neoplastic disease Heart failure Cerebrovascular disease Renal disease Liver disease Physical findings Altered mentation Respiratory rate $\geq$ 30/min Systolic BP $<$ 90mmHg Temp $<$ 35^{O}or $\geq$ 40^{O}C Pulse $\geq$ 125/min Lab findings pH $<$ 7.35 BUN $\geq$ 30 mg/dl Sodium $<$ 130 mmol/L Glucose $\geq$ 250 mg/dl Hematocrit $<$ 30% Pulse oximetry $<$ 90% Pleural effusion on X-Ray	Confusion Urea ($>$ 19 mg/dl) Resp rate $\geq$ 30 /minute Blood pressure $<$ 90 mmHg systolic or $\leq$ 60 mmHg diastolic Age $\geq$ 65 years	Major: Mechanical ventilation; Vasopressor therapy Minor: Resp rate $\geq$ 30 PaO2/FiO2 $\leq$ 250 Multilobar infiltrates Confusion BUN $\geq$ 20 mg/dl WBC $<$ 4000 cells/μl Platelet $<$ 100 000/ μl Hypotension requiring fluid support Hypothermia $<$ 36^{O}C	Systolic BP $<$ 90 mmHg Multilobar Albumin $<$ 3.5 g/dl Resp rate $\geq$ 25 ($\leq$ age 50; $\geq$ 30 ($>$ age 50) Heart rate $\geq$ 125/min Confusion SaO2 $<$ 93 if ($\leq$ age 50); $\leq$ 90% ($>$ age 50) Ph $<$ 7.35	Major: pH $<$ 7.30 BP $<$ 90 mmHg Minor: Confusion Ureas $>$ 30 mg/dl Resp rate $>$ 30 Multilobar bilateral $PaO_2 < 54$ mm Hg or $PaO_2/FiO_2 < 250$ Age $\geq$ 80 years
Comments	2 step process; points assigned to variables; I-V Risk Class V for inpatients 30-day mortality of 27.1%	Mortality: 3 variable 17% 4 variable 41.5% 5 variables 57%	'ICU admission recommended if 1 major or 3 minor criteria. Mortality if 3 criteria 15.6% Li *et al.* Medicine 2015; 94: 1–7)	Designed to identify need for mechanical ventilation or vasopressor therapy; points assigned to variables. If $\geq$7 points 30-day mortality 33.3%	Designed to identify patients at increased risk of complicated community-acquired pneumonia evolution. Weighted points assigned to each variable. If 20–30 points 42% have sCAP; 30 or higher 50%

CAP, community-acquired pneumonia; PSI, Pneumonia Severity Index.

CURB-65 was slightly better in early mortality prediction and in predicting admission to intensive care support [28▪]. In a systematic review of 40 studies, Chalmers *et al.* reported no significant difference in predicted 30-day mortality between PSI and CURB 65. The area under the summary receiver operator characteristic curve (sROC) was 0.81 for PSI and 0.80 for CURB 65. The calibrated risk ratios (RR) for the highest severity scores for PSI (V) and CURB-65 (3–5) were 0.99 (0.88–1.11) and 1.03 (0.84–1.25), respectively [29]. While all of these prediction scores have been utilized for severe CAP, SMART-COP., SCAP and ATS/IDSA criteria are more specific for predicting requirement of ICU care and short-term mortality for sCAP. There is no consensus on the optimal assessment tool or how it should be applied for sCAP as there is significant heterogeneity of patients admitted to the ICU in different settings (especially in the absence of need for mechanical ventilation or shock). Thus, these scoring systems should primarily serve as a supplement to clinical judgment. Furthermore, performance of CAP mortality scores is suboptimal in many patients since there is often a discrepancy between initial acuity of illness (i.e., severity) and mortality. Many metrics of severity such as pulse, respiratory rate and BP may be quickly reversible depending on appropriate management and host factors.

Clinical experience suggests the ATS/IDSA criteria correlates reasonably well for predicting need for ICU admission and short-term mortality [30]. Despite this, recent studies indicate that accuracy is variable. Cavallazzi *et al.* in an assessment of hospitalized patients found that 9% who did not meet the ATS/IDSA criteria for ICU admission were admitted to the ICU and of the patients who met ATS/IDSA criteria 44% were admitted to ICU [14]. Among patients in the ICU, the in-hospital mortality rate was 11% for patterns who did not meet ATS/IDSA criteria and 19% for patents who met the criteria. Various modifications of the ATS/IDSA criteria have been assessed with some showing better accuracy [31–33].

The ATS/IDSA minor criteria are especially valuable to identify patients who have potentially severe disease but who do not immediately meet the major criteria for admission to an ICU such as need for mechanical ventilation or vasopressor therapy but are at high risk of deterioration and subsequent ICU admission and death [34]. The ATS/IDSA minor criteria can be overly sensitive, nevertheless, they can be helpful to identify high-risk patients for

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early consideration of critical care management. It is well recognized that admission to a general ward setting with later transfer to the ICU may delay proper intervention and increase mortality [35]. Identifying high-risk patients is crucial to allow optimal early management.

Biomarkers

Biomarkers that specify inflammation or are associated with lung injury CAP may be an effective way to identify patients with sCAP and follow the course of infection during ICU admission. Procalcitonin (PCT) and C-reactive protein (CRP) are most commonly used to follow patients with sCAP and have played an important role in antimicrobial stewardship by assisting the decision for duration of therapy and thereby helping to reduce the duration of antimicrobial therapy. PCT has the advantage of elevating earlier and being timelier in response to therapy.

In a multicenter study, Ito *et al.* observed serial measurements of PCT were useful in predicting the prognosis and treatment efficacy, as well as in the assessment of pneumonia severity and was more useful than CRP as a biomarker [36]. In another multicenter study Self *et al.* found that serum PCT concentration was strongly associated with the risk of requiring invasive respiratory or vasopressor support among adults hospitalized with CAP and is potentially useful for guiding decisions about ICU admission [37]. One meta-analysis of randomized trials in critically ill patients found a significant reduction in mortality with the use of PCT guidance [38].

Other biomarkers which have been variably assessed for CAP including IL-6, D-dimer, Prespesin, and adrenomedullin [39]. More recently there has been the emergence of metagenomics for which the diagnostic and predictive value warrants further study.

RISK FACTORS AND ASSESSMENT OF LONG-TERM MORTALITY

Age and comorbidities

Advance age at the time of hospital admission due to an episode of CAP have been reported in several studies as a risk factor for long-term mortality [6,7,40–42]. Our data from Louisville show a one-year mortality rate of 30% among the full population of hospitalized patients with CAP. This rate increases to 38% in patients aged 65 years or older [42].

The presence of multiple comorbidities at time of hospitalization has been linked to increased long-term mortality [7,41–43]. The primary comorbidities identified include COPD, heart disease, diabetes, and neurological diseases. Accumulation of comorbidities has been recognized as a risk for long-term mortality in patients older than 50 years in a French cohort [12]. Similarly, our Louisville data on long-term mortality documented an increase in long-term mortality in patients with comorbidity staking (Fig. 1) [42].

COPD also plays a significant role in the etiology of death post discharge in patients hospitalized with CAP. A study from Norway, which followed consecutive patients hospitalized with CAP over five years, identified COPD as the primary cause of death after hospital discharge, followed by cardiovascular disease [41].

Inflammatory response

The systemic inflammatory response observed during the acute episode of CAP has been associated with long-term mortality. Research has shown that, despite clinical recovery, many patients with CAP are discharged from the hospital while experiencing ongoing inflammation [44]. The authors reported an increased risk for long-term mortality in patients with elevated levels of interleukin (IL)-6 and IL-10 levels at time of hospital discharge. It is considered that this residual low level chronic inflammation is driving the increased risk of long-term mortality.

Another study reported that patients with by a history of chills, elevated body temperature and high peak levels of the inflammatory marker CRP have better long-term outcomes [45]. These observations suggest that an appropriate initial physiologic response during hospitalization correlates with improved long-term survival. Conversely, a persistent low-level inflammation after hospital discharge is associated with reduce survival.

Severity and clinical course

The severity of CAP and the clinical course of patients during initial hospitalization are associated with survival after hospital discharge. In a study conducted in Louisville, we compared the one-year mortality rates among the general population of hospitalized patients with CAP to those with severe CAP or a poor clinical course, defined as patients requiring ICU care versus the population of CAP patients who had a favorable clinical course, defined as patients reaching early clinical stability. The one-year mortality rate for the general CAP population was 30%, which increased to 47% in CAP patients requiring ICU care and decreased to 24% in CAP patients who reached early clinical stability [42]. One challenge in evaluating long-term mortality in special populations hospitalized with pneumonia

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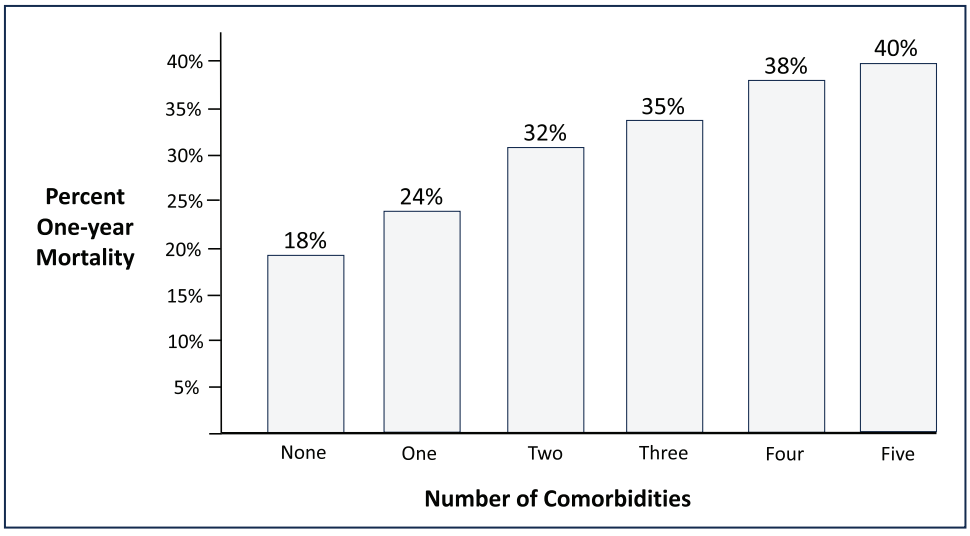

FIGURE 1. One year mortality after hospitalization for patients with CAP by number of comorbidities. CAP, community-acquired pneumonia.

is the lack of control subjects. Patients hospitalized for any reason who are admitted to the ICU or are immunocompromised are more likely to die. In these special populations, it is difficult to discern the real impact of pneumonia on overall mortality.

Immunocompromised host

Patients who are immunocompromised have been reported to be at high risk for long-term mortality [41]. In our Louisville study, we observed a gradient in long-term mortality corresponding to the degree of immune function impairment in hospitalized patients with CAP. We categorized the population of hospitalized patients with CAP based on their immune function as patients with normal immune function, patients with abnormal immune function, patients who are immunocompromised, and patients who are severely immunocompromised. The one-year mortality for each of the groups is depicted in Fig. 2 [42].

In a prospective observational study from the Netherlands, which evaluated the causes of death following the initial recovery from an episode of CAP, investigators identified malignancy as the primary cause of death, follow by COPD and cardiovascular disease [7].

Scores to predict long-term mortality

The primary scores for defining short-term mortality in patients with CAP are the PSI and CURB-65 [10,23]. Our group evaluated the overall performance of the PSI and CURB-65 in their ability to predict long-term mortality in hospitalized patients with CAP who were discharged alive after recovering from the acute episode of CAP. We conducted a receiver operating characteristic analysis to calculate the area under the curve (AUC) for both PSI and CURB-65 to evaluate their ability to distinguish patients who will be alive or dead one year after discharged alive. The AUC for the PSI was 0.72 and for CURB-65 was 0.66 [46]. Although the PSI may slightly better predict long-term mortality in patients with CAP, both scores exhibit limited predictive capacity.

Future research directions

At the present time there are no effective tools to accurately predict long-term survival in hospitalized patients with CAP. A working group of pneumonia investigators assembled by the National Institutes of Health to prioritize areas of pneumonia research, identify the need to develop methods that will discriminate those CAP patients likely to decline over time and die from other CAP patients with a more favorable course [1].

Although the PSI offers a better predictive capability for long-term mortality than the CURB-65 score, there is a critical need for advancements in the precision of the PSI for individual patient risk stratification. As data accumulate on the different risk factors associated to long-term mortality, these clinical and laboratory parameters can be used to improve the PSI or to develop new prediction scores focusing on postdischarge outcomes.

Another research approach is to develop new prediction models using artificial Intelligence (AI). Predictive models using AI can integrate a broad spectrum of data, including patient demographics, clinical history, laboratory and imaging results,

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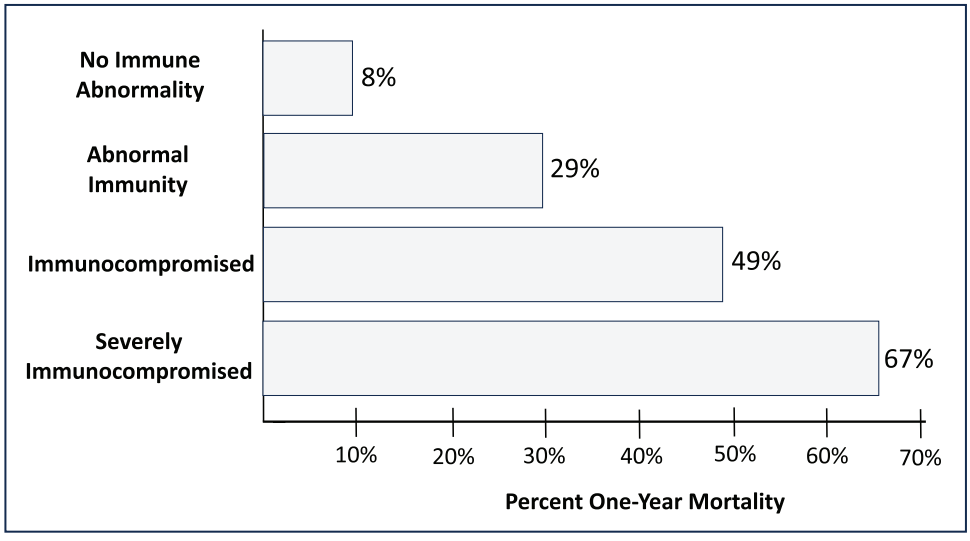

FIGURE 2. One year mortality after hospitalization for patients with CAP according to function of immune system. CAP, community-acquired pneumonia.

microbiological findings, treatment modalities, and clinical outcomes during hospitalization. Developing models with a comprehensive dataset approach are likely to enhance the predictive accuracy for short-term and long-term survival.

The development of an optimal prognostic tool for postacute sequelae of CAP is imperative for identifying specific populations at increased risk. Investigating the pathogenesis that leads to diminished survival in these groups is crucial, as it will inform preventive and targeted interventions. Moreover, accurately identifying at-risk populations is essential for their inclusion in clinical trials that evaluate potential therapies designed to improve long-term clinical outcomes.

CONCLUSION

CAP is a multisystemic disease with the potential to cause both acute and long-term sequelae, significantly impacting patient mortality rates. In clinical practice, we have good prediction scores to assess a patient risk for need of ICU care and risk for short-term mortality. On the other hand, for patients who are discharged alive from the hospital, we do not have good scores to predict long term mortality.

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Conflicts of interest

There are no conflicts of interest.

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